UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: *Wave 8 Cases*	

GENERAL REPORT OF MILES MURPHY, MD MSPH FACOG

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I. BACKGROUND

I am a medical doctor licensed in the state of Pennsylvania. My education and employment history can be found in my curriculum vitae (CV) found as Attachment 1. In summary, I earned my medical degree from the University of Pittsburgh in 1997. Upon graduating, I began my four-year residency in Obstetrics and Gynecology (Ob/Gyn) at Lehigh Valley Hospital, which I completed in 2001. Following that I completed a three-year fellowship in Female Pelvic Medicine & Reconstructive Surgery (a.k.a. Urogynecology) at the University of Louisville. I completed this program in 2004, at which time I also earned a Masters of Science in Public Health (MSPH).

In July of 2004, I began my practice as the Associate Medical Director of the Institute for Female Pelvic Medicine & Reconstructive Surgery, a position that I still hold. I received my board certification from the American Board of Obstetrics and Gynecology in 2006, and in 2008 I became the Director of the Division of Urogynecology at Abington Memorial Hospital and an Assistant Clinical Professor of Obstetrics and Gynecology for the School of Medicine at Temple University. In 2013 I received my sub-specialty board certification in Female Pelvic Medicine & Reconstructive Surgery (formerly known as Urogynecology). 2013 was the first year that this certification became available, and to the best of my knowledge, there are less than 1000 physicians in the U.S. with this subspecialty board certification.

I have served on the Scientific Program Committee for the American Urogynecologic Society (AUGS) for multiple years. This society is considered by most specialists in the field of

Female Pelvic Medicine & Reconstructive Surgery (FPMRS) to be the preeminent society of this specialty. I served as the Program Chair of the 2015 Annual Scientific Meeting of AUGS. Finally, I served as the Chair of the Clinical Practice Council of AUGS from 2015 -2017. As chair of this council I oversaw the Coding Committee, the Guidelines & Statements Committee, the Systematic Review Committee, and the Alternative Payment Committee of AUGS. In addition to my work with AUGS, I have been substantially involved with the Society of Gynecologic Surgeons (SGS). I currently serve on the Executive Committee of the Board of Directors as the Secretary/Treasurer of SGS. This society is dedicated to promoting "excellence in gynecologic surgery through acquisition of knowledge and improvement of skills, advancement of basic and clinical research, and professional and public education." I served as the Chair of the Research Committee of SGS from 2013 - 2016. During this time I oversaw the Fellows Pelvic Research Network and the SGS Systematic Review Group (SRG). The mission of the SGS SRG is "To systematically review the important subjects and controversies in the field of gynecologic surgery and to produce evidence-based clinical practice guidelines." As such, I am well-versed in systematically reviewing the existing data on a given clinical topic and drawing conclusion from that review. This knowledge of systematic review has informed my preparation of this report.

My practice is a subspecialty practice consisting entirely of women with disorders of the pelvic floor. The vast majority of patients that I treat present with urinary incontinence (UI), pelvic organ prolapse (POP), or a combination of the two. I perform approximately 5 – 8 urogynecologic surgical cases per week and have done so for the past 17 years (the first three years in fellowship). The majority of the surgeries I perform are for a combination of pelvic organ prolapse and urinary incontinence, but I would estimate that approximately a quarter of the

surgeries I perform are for incontinence alone. I perform procedures both for stress incontinence and for urgency urinary incontinence. I first began performing midurethral slings (MUS) when I was a resident in Ob/Gyn in the late 1990's. The Tension-Free Vaginal Tape (TVT) was one of the first MUS's to be marketed in the United States. Since completing my residency in 2001 I estimate that I have performed over 3000 MUS's.

A list of materials that I have reviewed that are pertinent to the subject of the treatment of urinary incontinence and this case, in particular, can be found in the attached bibliography.

II. URINARY INCONTINENCE

Types of Urinary Incontinence

Urinary incontinence can occur in men and women. This report will be limited female urinary incontinence and the ways in which it is treated. There are three major forms of urinary incontinence (UI) in women: stress urinary incontinence (SUI), urgency urinary incontinence (UUI), and mixed urinary incontinence (MUI). SUI is defined by the International Continence Society (ICS) as complaint of involuntary loss of urine on effort or physical exertion (e.g. sporting activities), or on sneezing or coughing. The ICS defines UUI as complaint of involuntary loss of urine associated with urgency (the complaint of a sudden, compelling desire to pass urine which is difficult to defer). When a patient suffers from MUI, she has symptoms of both SUI and UUI (Haylen 2010). There are other types of UI: coital, postural, continuous, and insensible incontinence. These types of UI are much more rare than SUI, UUI, and MUI. The TVT device was designed to treat SUI.

Prevalence of SUI

SUI is a highly prevalent condition that over 15% of women in the United States suffer from (Nygaard 2008). The annual direct cost of urinary incontinence in women in the United States (1995 dollars) was estimated as $12.4 billion and the largest cost category (70% of the cost) was routine care (Wilson 2001). These facts underline the importance of an effective surgical cure of this condition that can theoretically greatly reduce healthcare expenditures in the U.S. on this problem by eliminating the need for routine care (i.e. pads, anti-deodorants, etc.).

Treatment Options for SUI

Non-Surgical Treatment Options for SUI

SUI is a condition that is not life-threatening; however, it often negative impacts a patient's quality of life. This impact can be at its minimum, annoying; and at its maximum, devastating to a patient's well-being. As such, it is a condition that can be managed in one of three ways: expectant management, conservative management, and surgical management. Expectant management refers to a "watch and wait" course of action (in a more pessimistic view, "doing nothing"). In relatively rare situations, most commonly the pregnant or post-partum state, SUI will spontaneously resolve without intervention. In most situations, however, the condition will either stay the same or worsen as time goes by.

The two most common forms of conservative treatment of SUI are pelvic floor muscle therapy (PFMT – a.k.a. Kegel exercises) and insertion of anti-incontinence pessary devices. Pessaries are usually used to treat pelvic organ prolapse (POP), but special types of pessaries have been designed to treat SUI. Anti-incontinence pessaries can be used in any willing patient with SUI, but I find the patients that are the best candidates for this form of therapy are patients who suffer from SUI but have not yet completed their child-bearing. Although there are reports of patients having anti-incontinence surgery, becoming pregnant afterwards, and successfully carrying to term; there is a concern that the repair in these patients can be compromised by delivery resulting in recurrent SUI.

The other common form of conservative management of SUI is PFMT. PFMT involves contraction of the pelvic floor musculature. The major muscle group flexed in this exercise is the levator ani complex. These are skeletal muscles under voluntary, conscious control.

However, the very things that lead a woman to develop SUI – namely pregnancy and delivery – can also lead to an inability to contract these muscles. These include avulsion of these muscles from their bony attachments and neurologic injury to the nerves that innervate these muscles. In patients with such injury, PMFT can be a futile exercise. PMFT can either be performed on a patient's own or under the supervision of a pelvic floor physical therapist or some other health-care professional with adequate training in these techniques. However, even under supervised therapy with a physical therapist, up to 50% of women who are initially treated with PFMT eventually opt for surgical correction of their UI (Bo 2005).

Multiple single-arm studies of this type of intervention have shown a significant improvement in SUI symptoms in patients who undergo PFMT (Imamura 2010). The data suggests that patients do best when enrolled in a supervised program. However, even under strict instruction within a clinical trial, subjects do not fare as well as those who undergo surgery. The most recent study to demonstrate this disparity is a randomized clinical trial (RCT) published in the New England Journal of Medicine (Labrie 2013). This study of 460 Dutch women randomized patients to either physiotherapy under the direction of 478 certified pelvic floor physical therapists or surgery (TVT or TVT-O) performed by one of 49 gynecologists or urologists. The rates of subjective cure were 85.2% in the surgery group and 53.4% in the physiotherapy group (absolute difference, 31.8%; 95% CI, 22.6 to 40.3); a highly significant difference favoring MUS surgery.

Suture-based Repairs of SUI

There are a number of suture-based repairs for the treatment of SUI. The term "suture-based" is used to describe procedures that rely on a combination of the patient's own tissue and

either absorbable or permanent suture material to correct the patient's SUI. This term is used to differentiate this type of repair from a sling repair. With sling surgery, the surgeon utilizes some type of graft material placed under the patient's urethra to correct her SUI. I will elaborate on the different types of graft materials that can be used to create slings later in this report.

The Kelly plication was the predominant surgical procedure performed for SUI in women during the first half of the 20th century. The Kelly plication involves plicating the connective tissue under the urethra. In 2007 the American College of Obstetrics and Gynecology (ACOG 2007) published a Practice Bulletin that states, "For women with positive prolapse reduction stress test results who are planning vaginal prolapse repair, TVT midurethral sling (rather than suburethral fascial plication) appears to offer better prevention from postoperative stress incontinence."

Kelly plication was overwhelming replaced by retropubic urethropexy (RPU) in the 1950's, as the popularity of the Burch and Marshall-Marchetti-Krantz (MMK) procedures spread across North America. RPU surgery was traditionally performed as an "open" abdominal procedure, although in later years it was often performed as a "laparoscopic" abdominal procedure. The MMK procedure involves suturing the periurethral tissue at the level of the bladder neck to the posterior aspect of the pubic bone. This procedure, particularly in the past, was one commonly performed by urologists. The other common form of RPU is known as a Burch procedure. This procedure, historically favored more by gynecologists, involves placing a suture bridge from the periurethral tissue to the iliopectineal ligaments to stabilize the bladder neck. One risk of RPU's is the development of a painful inflammation of the periosteum, bone, or ligaments of the structures of the anterior pelvic girdle known as "osteitis pubis". This occurs more commonly after the MMK procedure than the Burch procedure.

While the MMK and the Burch were relatively successful at correcting SUI (especially in short-term studies), as trans-abdominal procedures, they were also relatively invasive surgeries. In an effort to decrease the invasiveness of anti-SUI surgery, a number of surgeons began work on developing what became known as "transvaginal needle-suspension" procedures. The first of these was first described by Pereyra in 1959, but many modifications were developed often eponymously named by their inventor: these include the Stamey, Raz, Muzsnai, and Gittes procedures. These procedures eventually fell out of favor, to the extent that while there is a section on these procedures in the second edition of a popular urogynecology textbook (Walters & Karram, 1999); this section was removed from the third edition (2007).

Grafted Repairs of SUI

There are many studies that suggest that the integrity of the connective tissues in many women with pelvic floor dysfunction are weaker than the connective tissues of women without pelvic floor dysfunction (Norton 1992, Boreham 2002). This holds true not only for women with POP, but for those with UI as well (Gilpin 1989, Ulmsten 1987). As such, the field of FPMRS has turned to materials (grafts) to augment the repair of connective tissue that is often deficient in the women who suffer from pelvic floor dysfunction. Grafts used in pelvic reconstructive surgery can be divided into two basic types: *biologic and synthetic*.

Biologic Grafts

Biologic grafts can be autologous, heterologous, or xenogenic. Autologous grafts are harvested from and then implanted in the same patient. The most commonly known examples of this type of graft are the fascia lata and rectus fascia grafts that are harvested from women with SUI and fashioned into suburethral slings. Since these grafts come from the patient herself there

is very little risk of a foreign body reaction or transmission of infection. However, autologous grafts may produce morbidity at the harvest site and procurement of the graft adds operative time and the potential for increase blood loss to the reconstructive procedure. Heterologous grafts (a.k.a. allografts) are materials harvested from a human donor other than the patient herself. Allografts are usually harvested from cadavers and processed with solvent dehydration or freeze-drying. Since morbidity from the harvest site is not a concern with cadaveric material, some surgeons prefer using allografts when using a biologic graft for reconstructive pelvic surgery.

The other type of biologic graft is a xenograft. These are materials that are harvested from other species and processed for use in humans. Due to the risk of rejection and infection, these products are usually processed into acellular collagen scaffolds. In some of these grafts the collagen is cross-linked to minimize degradation by host collagenases. The most common forms of xenografts used in pelvic reconstruction are porcine and bovine derivatives.

While the concept of suburethral support was originally introduced in 1907 by Giordano, it was not until its reintroduction in 1978 by McGuire and Lytton that it gained increased clinical use. Since this initial description a number of different techniques for securement and sling materials have been used, but the performance of the traditional "pubovaginal sling" has had only minor modifications since 1978 (Morgan 2000). The term **pubovaginal sling** will be used in this report to refer to the traditional type of sling that is placed at the bladder neck (the area underneath where the bladder and the urethra meet). This is to differentiate this type of sling from a midurethral slings, such as the TVT.

In the case of an autologous pubovaginal sling, a 6 to 8 X 1 to 1.5 cm portion of the rectus fascia is harvested through a Pfannenstiel incision and secured at the ends with suture. An

inverted U or midline incision is centered over the proximal urethra, and the endopelvic fascia is sharply perforated lateral and distal to the bladder neck thus entering into the retropubic position. The sling sutures are passed from the vaginal to the abdominal incision lateral to the rectus muscle and then tied across the midline over the rectus fascia with the least amount of tension required to prevent urethral motion.

Early series of 67 women undergoing autologous fascial slings revealed very good results with a cure rate of 82% and another 9% improved at a mean follow-up of 3.5 years (Blaivas 1991). Most of the failures were felt to be the result of urge incontinence. A later, much larger series of almost 250 women noted similar cure rates with favorable responses to the short form of the Urinary Distress Inventory (UDI-6), a validated, condition-specific quality of life instrument (Morgan 2000). In this series there was a <1% incisional hernia rate and no sling erosions.

Despite these good results, in an attempt to minimize the invasiveness of the procedure and to limit harvest-site morbidity, many surgeons moved towards allogenic grafts for their suburethral slings. One early series of sixteen women undergoing sling surgery using allogenic human cadaver fascia lata showed acceptable short-term results (Handa 1996). They reported an objective success rate 79% at follow-up ranging from 6-12 months. The mean duration of postoperative bladder drainage was 29 days.

Longer term follow-up in other similar series, however, showed less favorable results. Failure was noted in 52% of patients, with recurrent SUI symptoms occurring from 2 weeks to 24 months (median 3months) after the procedure (Fitzgerald MP 2004). Results are not significantly better when bone anchors are used to anchor the sling into the posterior aspect of

the pubic bone. One study showed recurrent SUI in 37.6% of patients at 10.6 months of follow-up using freeze-dried fascia (Carbone JM 2001) and another using non-frozen solvent-dehydrated fascia showed recurrent SUI in 37% of patients at 24 months (Nazemi 2008). Furthermore, there appears to be a relatively high erosion rate with cadaveric fascia. Within as little as 45 days, one study showed a 23% vaginal erosion rate (Kammerer-Doak 2002).

Fitzgerald et al theorize recurrent SUI in patients treated with freeze-dried irradiated fascia *allograft* sling may be the result of material failure. They note that on reoperation, the graft was either grossly degenerated (6%) or completely absent (14%) in up to 20% of patients (Fitzgerald 1999). On the other hand, this same group of investigators note in a smaller series of patients with *autologous* rectus fascia slings, that these slings remain viable. There appears to be proliferation of fibroblasts, neovascularization, and remodeling of the graft with no evidence of an inflammatory reaction or graft degeneration (Fitzgerald 2000).

Synthetic Grafts

Synthetic grafts have traditionally been categorized by a classification system first described by Amid in regards to abdominal hernia repair (Amid PK 1994). Synthetic implants can be made from knitted single-fiber filaments (monofilament materials) or they can be braided with monofilament yarns, further woven as multifilament fibers in different ways and pore sizes.

Multiple factors influence the suitability of mesh for human use: the degree of inflammatory reaction is related to its chemical composition and the amount of material used, flexibility of the mesh can affect organ function, and strength can be related to the durability of the repair. One of the critical categories in the Amid system is pore size of the mesh, which has

been related to infectious risk and fibroblast infiltration. Bacteria, which can measure as little as or less than 1 micron in size, easily enter into synthetic meshes. However, larger pore sizes are required to allow passage of leukocytes (9-15 µm in size) and macrophages (16-20 µm in size). In general, knitted materials have greater porosity than woven materials (Chu 1985). Interstices between multifilament fibers is also important, in that those with interstices of less than 10µm may theoretically allow passage of bacteria but not the cells from the host's microbial defense system. Pore sizes >75µm can allow for rapid ingrowth of fibroblasts (50µm) and vascular elements necessary to anchor the implant within the native tissue (Deprest 2006). The vast majority of synthetic grafts currently used for the treatment of SUI are Amid Type 1 polypropylene mesh. Type 1 meshes are by definition macroporous (pore size >75µm) and monofilamentous.

Following the rebirth of the autologous pubovaginal sling surgery for the treatment of SUI in the 1970's, a number of synthetic slings were also investigated. One of the first non-biologic materials used for SUI was woven polyethylene (Mersilene)(Nichols DH), but this multifilamentous material was, in some cases, associated with significant complications such as delayed transection of the urethra (Melnick 1976). Other synthetic materials used in procedures for SUI that did not ultimately prove ideal for vaginal use included the "Teflon tape suspension,"(Cato 1981) the "Marlex"(Morgan JE) and the "Silastic"(Stanton 1985) sling operations.

In the 1980's a number of surgeons started using polytetrafluoroethylene (Gore-Tex) for their pubovaginal slings. Short-term objective and subjective cure rates were good at 85%, but even at this 3 month post-operative evaluation complications such as urinary retention and wound seromas were noted (Horbach 1988). Longer follow-up studies showed that voiding

difficulties often required prolonged catheterization and/or sling revision; in some cases, even sling removal did not relieve these patients' urinary retention (Weinberger 1996). One study of patients who were at least one year out from surgery showed post-operative wound complications in 40% and noted that 22% of the grafts were eventually removed (Weinberger 1995). In a 1997 review of the use of mesh in gynecologic surgery, Iglesia et al concluded that "The ideal synthetic mesh material for pelvic surgery, one that induces minimal foreign-body reaction with minimal risk of infection, rejection and erosion, has yet to be developed." (Iglesia 1997)

It was around this time when surgical device manufacturers began to market pre-packaged slings. A number of various materials were used in an attempt to avoid the complications associated with other synthetic slings. One of the first was a woven polyester sling treated with pressure injected bovine collagen (ProteGen, Boston Scientific, Natick Massachusetts). This device was recalled in January 1999. One multicenter study reported on 34 patients who had undergone removal of the polyester slings within the two previous years (Kobashi KC 1999). **The average patient in this study presented within 8 months of original sling placement.** Of the 34 women, 17 (50%) had vaginal erosion only, 7 (20%) had isolated urethral erosion, and 6 (17%) had urethrovaginal fistula. Another polyester mesh sling, this one coated with silicone (American Medical Systems) was noted to have similar problems in a premarket, multicenter trial (Govier 2005). Ten of thirty-one (32%) required a second surgical procedure at an average of 6 months (range 68 to 343 days) postoperatively. Eight (26%) had vaginal extrusion of the mesh, one required sling lysis, and one required sling removal because of infection. This product was subsequently not marketed in the United States. It is not entirely clear why these devices had such high erosion rates, but one study of polyester and

polypropylene meshes removed for erosion showed bacterial contamination in all cases (Boulanger 2008). The majority of cultures demonstrated multimicrobial growth, but when only one bacterium was found, it was Proteus mirabilis in 25% of cases. However, bacterial quantifications varied greatly and because quantification was often low, the authors concluded that the role of bacterial contamination in mesh erosion "is not yet clear."

Polypropylene meshes have been used in humans for over 50 years to correct connective tissue defects. Some of the earliest data on such use was published in 1958 and supported the use of this material for the repair of incisional hernias (Usher 1958). By the 1990's the use of synthetic polypropylene mesh for repair of abdominal wall hernias was becoming very common. Its use was supported by a randomized clinical trial conducted in the late 1990's and published in the New England Journal of Medicine in 2000 (Luijendijk 2000). By the turn of the millennium, polypropylene mesh was the considered by experts in the field to be the best graft material to use in hernia repairs (Scott 2002, Burger 2004, Cobb 2005). As the next section of this report will show, this material is also what was ultimately used in the tension-free vaginal tape.

III. HISTORY OF THE TVT AND TVT-O

Creation of the TVT

Prior to the creation of the TVT, the majority of physicians who treated women with SUI felt that their incontinence was the result of either an intrinsic weakness (or deficiency) of the urethral sphincter muscles (ISD) or a lack of support at the bladder neck known as urethrovesical junction (UVJ) hypermobility. Therefor, most surgical treatments of female SUI focused their attention at the bladder neck. These procedures included both bladder neck suspensions (MMK, Burch, Raz etc) and traditional pubovaginal slings.

However, in the 1990 Peter Petros and Ulf Ulmsten proposed an alternative theory regarding the etiology of female urinary incontinence that focused its attention on support of the midurethra (Petros 1990). This "Integral Theory" of incontinence emphasized the complex interplay of specific structures within the vaginal wall including ligaments, muscles, and their connective tissue insertions. It also addressed the effects of age, hormones, and iatrogenically induced scar tissue on these structures. The theory relied on concepts that originated between the 1950's to the 1980's by clinicians such Ingelman-Sundberg (1957), Zacharin (1961), Ulmsten (1977), and Westby (1982).

This theory led Ulmsten and Petros to invent a new technique to treat SUI in women that came to be known initially as "Intravaginal slingplasty (IVS)". The technique was developed after experimental and clinical studies yielded what the authors felt was the best technique to restore the pubourethral ligament and suburethral vaginal hammock. The sling was placed at the midurethra (not the bladder neck), where they proposed the pubourethral ligaments were to have

their functional insertions. The sling was placed loosely – without elevation – around the urethra and the abdominal ends were not fixed. They published their results of this new ambulatory procedure after performing it in 50 patients (Ulmsten 1995). The results revealed that 90% of the patients were either cured or had considerable improvement in their urinary incontinence. No intra- or post-operative complications were noted.

Ulmsten continued development of the IVS concept, which led to even further refinement of his technique. This included a less extensive vaginal plasty requiring only a minor incision of the suburethral vaginal wall, and resulted in even shorter operative time. This technique also solely utilized large pore, monofilament, polypropylene mesh. Ulmsten viewed this material to be preferable to other permanent synthetic material that had demonstrated rates of adverse tissue reaction ranging from 9 - 23% (Falconer 1996, Bent 1993). These materials included polyester (Mersilene) and polytetrafluoroethylene (Gore-tex).

His views were supported by abdominal wall hernia mesh research (Amid 1994). This research revealed that synthetic grafts which contain pores or spaces less than 10 microns in any of their three dimensions can increase the chance of infection and sinus tract formation. Bacteria averaging 1 micron in size can hide in such spaces and be protected from neutrophilic granulocytes, which average 10 – 15 microns in size. Macroporous biomaterials with pore sizes larger than 75 microns, such as the monofilamented polypropylene mesh used in this new IVS procedure, do not promote or harbor infection. This is unlike microporous biomaterials with pores smaller than 10 microns, such as Gore-Tex and Mersilene; when these become infected, these materials often need to be removed. Indeed, when these materials were used in sling procedures they resulted in high erosion and infection rates (Weinberger 1995 & Kobashi 1999).

In 1996 Ulmsten published his landmark paper describing the prospectively studied results of this modified IVS (Ulmsten 1996). In addition to the use of monofilamented polypropylene mesh, this procedure differed from previous traditional sling procedures in three key ways: first – the sling was placed via a vaginal route rather than the traditional abdominal approach, second – the sling was covered by a plastic sheath to theoretically prevent contamination prior to placement, and third – the sling was placed at the level of the midurethra, loosely positioned, with the sling arms not fixed to a static structure.

Because the sling mesh was covered in a smooth plastic sheath during placement it allowed the sling to slide easily through the patient's tissues. However, once proper placement was confirmed the sheath was removed, exposing the sling mesh to the patient's tissue. The "nooks and crannies" of the mesh then left to interact with the patient's tissue in a Velcro-like fashion securing it in place. This friction effect was distributed along the whole length of the sling rather than at a single attachment site. This aspect of the procedure was unique among other contemporary and preceding procedures; rather than anchoring the sling to one isolated spot (i.e. a bone anchor in the back of the pubic bone or a suture tied around the anterior abdominal fascial wall), Ulmsten's sling was placed in a "tension-free" manner, thus giving birth to its name. This procedure came to be known as the tension-free vaginal tape (TVT) (Ulmsten 1998). This basic sling material and method of placing it remains the gold-standard for the treatment of stress urinary incontinence to this day (Ward 2009, Ogah 2009, Iglesia 2012).

The first prospective investigation of the TVT procedure followed 75 patients for two years postoperatively (Ulmsten 1996). Pad tests and quality of life assessments were carried out pre- and postoperatively. Mean operative time was 22 minutes. There were no intra- or postoperative complications. Eighty-four percent of these patients were cured at the two-year

evaluation. An additional 8% were significantly improved. There was no significant improvement in SUI symptoms in the remaining 8% of patients. Of note, less than 7% of patients needed a catheter placed in the immediate postoperative period due to urinary retention. All of these patients were able to successfully void the next day. There were no defects in incisional healing or rejection of the sling. As these results were highly promising, Ethicon and ultimately Gynecare took interest in this surgical system/devise.

TVT: Transition to a Medical Device Marketed by Gynecare

Members of the European branch of Ethicon first visited Sweden to discuss this new surgical technique with Professor Ulmsten in 1995 according to a document written by Dr. Axel Arnaud on July 12th 2000 entitled "The History of TVT". Arnaud met with Ulmsten in November of 1995 during which time he was able to discuss the technique and attend four surgeries. He was impressed with the procedure and set about confirming this initial positive impression.

To that end he arranged for a number of prominent European experts in female urinary incontinence to visit Professor Ulmsten in Sweden so he could ask their opinions regarding the viability of this new devise and surgical technique. The general opinion was that the technique was excellent, despite the fact that the underlying concept challenged the current concepts of the time regarding the pathophysiology of SUI.

Given this positive feedback, he traveled to the Ethicon headquarters in New Jersey following year and met with members of the New Business and Research & Development teams. Shortly after this meeting the head of Ethicon European Marketing, Jacques Dumont, received

the green light from Ethicon's Chairman to proceed with a deal that would allow them to start marketing this new surgical system developed by Professor Ulmsten. This deal was officially signed on February 14, 1997.

Following the signing of the agreement, a European team was created to prepare the market launch that included Arnaud, Ulmsten and members of the Marketing division. The product was officially given the name "TVT" and efforts were made to engage experts in the field regarding this new product.

In October of 1997 the American branch of Ethicon sent to the FDA a "Section 510(k) notification of intent" to market the TVT in the United States. In an FDA documented January 28th 1998, the FDA cleared the TVT device, and therefore gave Ethicon permission to market the device in the United States.

TVT: Initial Experience

The results of the first multi-center trial of TVT were published in 1998 (Ulmsten 1998). Six clinics in Finland and Sweden enrolled 131 women with genuine stress incontinence, who were followed for a minimum of 12 months. Mean operative time in this trial, 28 minutes, was only slightly longer than the previous trial, and success rates were even higher. Ninety-one percent of patients were cured and an additional 7% were significantly improved. Only 2% were considered failures. Resumption of normal voiding was again seen within 24 hours postoperatively in the vast majority of patients. There were two uncomplicated hematomas and one bladder perforation. There were no tape rejections. This was in contrast to other sling studies in the 1990's using different tape materials such as Teflon, Gore-tex, Mersilene, and

Marlex which demonstrated rejection rates of approximately 10% or more during a similar length of follow-up.

As surgeons outside of Scandinavia began using the TVT, more data became available. These studies attested to the external validity of the initial findings that came out of Sweden and Finland. These studies included a large prospective multicenter trial in Italy (Meschia 2001) and TVT registry conducted in Austria (Tamussino 2001). The Italian investigation followed 404 women for a median time of 21 months (range 12-35). The subjective and objective cure rates were 92% and 90% respectively. An additional 4% were significantly improved. Complications included a 6% bladder perforation rate, retropubic bleeding requiring re-operation in 2 (0.5%) patients, and a 4% voiding dysfunction rate. The authors concluded that the TVT procedure "is associated with a high cure rate and a low morbidity." In the Austrian investigation a total of 806 patients from 29 gynecology units in Austria were entered into the registry. They noted a 2% rate of intraoperative bleeding and bladder perforation in 4%. The authors concluded "the TVT operation has relatively quickly been used in combination with other operations, such as prolapse repair, and in patients with relapses after traditional anti-incontinence surgery. Despite its use under these more complicated circumstances, major complications appear to be rare." Other investigators were also soon able to attest to the multiple clinical circumstances in which TVT was effective.

The earliest investigations of TVT were in women with uncomplicated stress-predominant incontinence. However, new data would soon show that TVT was also effective in cases of intrinsic sphincter deficiency (ISD), recurrent SUI, and mixed UI. Rezapour et al (2001) reported in a prospective long-term study of 49 women with stress incontinence and ISD that TVT placement resulted in complete cure of 74% of these difficult clinical cases. An additional

12% were significantly improved and only 14% showed no improvement. Few complications were noted.

Study of another difficult clinical condition, recurrent SUI after failed traditional surgical procedures, also yielded very good results. One study of 34 women who failed either the Burch colposuspension, the MMK procedure, or periurethral bulking injections showed an 82% cure rate after TVT, with another 9% significantly improved (Rezapour 2001). Despite this challenging clinical situation (which included potential preoperative retropubic scarring), there were no significant intra- or postoperative complications.

The third challenging clinical situation investigated was mixed UI. One prospective study of 80 women suffering from mixed UI – they all demonstrated urodynamic SUI and urge incontinence concomitant with urethral relaxation – followed these women for a mean of 4 years after TVT (Rezapour 2001). At long-term follow-up, 85% of the patients were cured and another 4% significantly improved. As with the recurrent SUI study, intra- and postoperative complications were rare.

In remarking five years later on the original landmark 1996 TVT article, Professor Stuart Stanton from St. George's Medical School in London England concluded, "Since that first article, worldwide experience has testified in a remarkably uniform way to the subjective and objective success and complication rate of this procedure" (Stanton 2001). And since that time, TVT has become the most studied surgical procedure for female SUI. Long-term follow-up of TVT at seven (Nilsson 2004) and eleven (Nilsson 2008) years shows very little decline in efficacy over time with a 90% objective cure rate at greater than ten years out from surgery.

Furthermore, long-term study has shown no new mesh-related complications that were not encountered during the initial investigation of this devise.

Obturator Midurethral Slings and the Creation of the TVT-O

TVT paved the way for other minimally invasive, outpatient procedures for SUI. TVT demonstrated the benefits of using a graft that does not have to be harvested from other parts of the patient's body, thus sparing her the risks of graft-site morbidity. It showed that macroporous, monofilament polypropylene slings could be placed transvaginally with low risk of mesh erosion and infection. After TVT, it became clear that slings placed at the midurethra (rather than the bladder neck) can result in very high cure rates with low rates of post-operative voiding dysfunction and/or retention. The incredible success of the original TVT showed that innovation could yield great rewards in the treatment of SUI.

This type of innovative thinking led to the creation of what is now often referred to as the obturator midurethral sling. These obturator MUS's were very similar to the retropubic MUS in that they were placed transvaginal at the midurethra most-commonly using a macroporous, monofilament polypropylene sling initially covered in a plastic sheath prior to final setting. They differed in that rather than being placed in retropubic space through two small incisions in the suprapubic area, they were placed in the obturator space through two small incisions in the groin. This placement created a less acute angle of the sling under the urethra and led to passage through an area farther away from the bladder and bowel. While the original TVT had very low rates of complication, placement of sling in the retropubic space carried along with it a risk of bladder perforation. Innovators hypothesized that placement through the obturator space would

greatly reduce this risk. While much less common, retropubic passage also carried with it a risk of bowel injury (especially in patients with previous retropubic surgery) (Gruber 2006). Lastly, while bleeding and vessel injury is a risk with any surgery, it appeared that obturator slings might also decrease the very rare, but potentially serious risk of major vessel injury.

Obturator MUS's can be divided into two major types: those that are placed through bilateral skin incisions in the groin and passed towards a vaginal incision at the level of the midurethra (the so-called "outside-in" technique) and those that are passed from the vaginal incision out towards incisions in the groin (the so-called "inside-out" technique). The latter came to be known as the TVT-Obturator (or TVT-O for short). The "outside-in" transobutator MUS is often referred to as a TOT (short for TransObturator Tape). The first technique to be described in the literature was the TOT (Delorme 2001).

Early experience with both types of transobturator MUS's appeared to significantly decrease the risk of bladder perforation and essentially eliminate the risk of bowel injury, and the initial series of these procedures reported similar efficacy outcomes to the retropubic TVT (de Leval 2003 & Davila 2006). The majority of these transobturator MUS's used mesh similar to or the same as TVT, but one utilized a polypropylene graft prepared through a heat-welding process with smaller pore size than the TVT and was shown to carry a short-term erosion risk as high as 13% (Yamada 2006). Many device companies market outside-in TOT's, but to the best of my knowledge, the TVT-O is the only marketed inside-out transobturator MUS.

TVT-O: Initial Experience

The "inside-out" approach to a transobturator sling was first described by Professor Jean de Leval in 2003 (de Leval, 2003). Professor de Leval was interested in the transobturator approach to midurethral sling placement, and its potential for a decreased risk of lower urinary tract injury as compared to the retropubic approach. However, early reports of this technique utilizing an "outside-in" approach demonstrated that bladder injury was still a risk (Hermieu JF 2003). In the initial report of a novel "inside-out" de Leval describes the technique that allows this approach using newly designed surgical instruments. The actual sling material is the same as that used in the classic retropubic TVT (Gynecare, Somerville, NJ, USA), but the rest of the surgical equipment is new.

He describes three specific instruments that were created for the procedure: helical passers, plastic tubes, and an introducer. The *helical passers* are pairs of instruments specific for the left and right sides. They are stainless steel instruments comprising a spirally shaped section and a handle. The element supported by the helical passer is a polyethylene *tube* with a pointed distal end. It has a lateral opening, which allows the insertion of the spiral segment of the helical passer into its lumen. The proximal end of the tube is opened and it can be attached intra-operatively to the above-mentioned sling material. Finally, the instrument called the *introducer* is a stainless steel device that comprises two segments: a proximal tubular hollow segment and a distal, semi-circular, 7cm long gutter. The purpose of the introducer is to act as a "shoe-horn" that allows placement of the passer from the periurethral tissue through the obturator foramen while protecting the lower urinary tract from injury.

Not only does this manuscript describe these novel instruments and the technique for "inside-out" placement of this transobturator sling, but it also reports on the results of a series of 107 consecutive patients treated with this sling. The mean operative time for sling placement was 14 min (range: 7-20). There were no peri-operative complications. Specifically, no injury of the urethra, bladder, nerves, or bowel was noted. No significant (>100ml) intra-operative bleeding was noted and there no cases of vaginal wall perforation. All patients had a follow-up visit one month after surgery. In the 107 patients, one vaginal mesh exposure was noted and three (2.8%) patients had urinary retention, which were corrected in the immediate post-operative period under intravenous sedation. These revisions did not require the tape to be cut, only loosened, and none of the patients developed recurrent incontinence or fistula. Finally, one patient developed superficial vein thrombosis eight days after surgery with subsequent development of an abscess 10cm away from the exit skin incision that required drainage. She did well after that. After that case, de Leval decided to prophylactically administer perioperative antibiotics to all patients undergoing this procedure. This type of prophylaxis is now considered standard for all urogynecologic surgeries.

Following the success of this initial series of patients, de Leval and his colleagues embarked on a prospective study of 102 patients in March of 2003 (Waltregny D 2004). The vast majority of these patients underwent incontinence surgery alone, but 16 had concomitant prolapse repair as well. Mean operative time for the TVT-O procedure was 14 minutes. No patients experienced blood loss greater that 200ml, postoperative hematoma or visceral injury. One vaginal sulcus laceration was noted intra-operatively, which required suturing before tape insertion. Of those patients who initially enrolled in this study, 99 (97%) were available for one-year follow-up (Waltregny D 2006). The SUI complete cure rate was 91%. No patient sustained

a vaginal or urethral mesh/tape erosion. Four patients required sling release or section for postoperative voiding dysfunction. Urinary frequency and urge symptoms also significantly improved after the surgery.

Given the excellent initial results of this novel procedure, Ethicon Women's Health and Urology began commercially marketing a pre-packaged TVT-Obturator (TVT-O) surgical system (which included the sling housed in the plastic sheath which was attached to two disposable helical passers [left and right] and the introducer, also known as the "winged-guide"), in 2004.

Three-year data from the initial series of patients was excellent (Waltregny 2008). Of those 102 patients initially enrolled in this prospective study, 91 (89%) were available for follow-up at three years. No sling erosion or persistent pain was noted at this longer follow-up. A total of 4 patients (~4%) needed sling revision for voiding dysfunction. Cure and improved rates were 88.4% and 9.3% of patients, respectively. This was similar to the one-year data ($p = 0.55$). Quality of life questionnaires showed persistent improvement over pre-operative evaluations and there was no significant drop-off from the improvement seen at one year.

A large registry of the first wave of patients treated with the Gynecare-marketed TVT-O kits in France was published the same year (Collinet 2008). A total of 984 women from 86 centers across France were enrolled in the study. The overall perioperative complication rate was 2.2% - the most common was vaginal wall perforation (1.3%). The post-operative complication rate was 5.2 % - the most common was residual pain (2.7%). Vaginal erosion rate was less than 1%. The authors of the study concluded that the inside-out transobturator

transvaginal tape approach to the treatment of female SUI was a safe procedure. A new era in the treatment of SUI had begun.

Overall Adoption of TVT-Type Procedures

Surveys of urogynecologic professional societies have shown wide-spread adoption of some form of synthetic mesh repair by their surgeons for the treatment of pelvic floor disorders. As early as 2002, a survey of practice patterns of the International Urogynecological Association showed that more surgeons were using a synthetic midurethral sling as their procedure of choice for SUI than were using a suture-based colposuspension (Davila 2002). One survey of the American Urogynecologic Society showed that nearly all of its members use synthetic mesh for at least some of their reconstructive procedures for SUI and/or POP (Pulliam 2007). The most recent survey in 2013 revealed that >99% of the members of AUGS use midurethral slings (Clemens 2013).

IV. TVT: COMPARATIVE AND LONG-TERM DATA

According to the AUGS/SGS Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence (2014), there are greater than 2000 publications in the scientific literature describing the MUS in the treatment of SUI in countries. The MUS has been studied in a wide-variety of different populations all over the world as a treatment for different types of SUI. This data has lead the leaders of our subspecialty professional organizations to state, "No other surgical treatment for SUI before or since (the MUS) has been subject to such extensive investigation." Of the MUS's, none has been studied more than the original, retropubic TVT. Given such extensive data, it would be inefficient to try to list all of that data in this report. Instead I will focus on the most rigorous research: randomized clinical trials and long-term studies of the TVT.

TVT: Randomized Clinical Trials

One of the most effective ways to study a medical treatment or type of surgery is with a randomized controlled trial (RCT). No sling surgery has been studied with more RCT's than the TVT. There are a plethora of independent RCT's comparing the TVT to other surgeries for SUI including expectant management, suburethral plication, retropubic urethropexies (RPU's), and many other types of slings. A Cochrane Review of MUS (including TVT and other MUSlings) published in 2011 (Ogah) looked at 62 RCT's including over 7000 women, and concluded "synthetic suburethral slings are as effective as traditional suburethral slings, open retropubic

colposuspension and laparoscopic colposuspension in the short-term but with less postoperative complications."

I conducted a search using the Ovid search engine in April 2014 using the terms "TVT" or "Tension-free vaginal tape" and looked for overlapping articles that came up under a search for the terms "randomized controlled trial as topic", "randomized controlled trial", or "randomized". This search yielded 206 articles in the peer-reviewed literature. I then screened this list of titles and abstracts for those that reported on RCT's with TVT as one of the arms under investigation. I noted articles reporting on the same group of subjects at a different time point than the original study publication and excluded studies in which it appears the subjects were not appropriately randomized. I combined this list with key RCT articles I have collected in my office over time on SUI surgeries that may not have been found in my Ovid search. A full list of these all these 65 articles can be found in Appendix A. All told, I found over 50 RCT's reporting on unique populations of patients. In continuing to update this report, I drew on some additional RCT's that I became aware of following the July publication of an exhaustive systematic review of slings published by Schimpf et al on behalf of the Society of Gynecologic Surgeons Systematic Review Group (2014). Undoubtedly, by the time I serve this report, additional RCT's will have been published. The following section of my report will focus on the key RCT's from my initial search combined with the findings of the two above-mentioned published systematic review of slings.

TVT: Randomized Clinical Trials Comparing TVT to Non-Surgical Intervention

As mentioned earlier in this report, there are three basic options for women who are suffering from SUI: expectant management (a.k.a. "watching and waiting"), conservative management (a.k.a. non-surgical management), and surgical management (multiple, different options are available). There are RCT's comparing TVT to all these options.

The first option of expectant management was investigated in a multicenter, prospective RCT in Canada (Campeau 2007). In this study 69 women over the age of 70 were randomized to undergoing immediate TVT or to wait for 6 months before submitting to the same surgery. After six months the women who underwent TVT had significantly higher improvements in Quality-of-Life and Urinary Problem questionnaires than those who were randomized to expectant management. Furthermore, Patient Satisfaction scores were four times higher in the TVT group than in the control group. The authors conclude that surgical treatment of SUI with TVT is, "better than no treatment."

The second option of conservative management has also been investigated in a multicenter, prospective RCT (Labrie 2013). This Dutch study published in the New England Journal of Medicine randomized 460 women to receive either pelvic floor physical therapy (physiotherapy, a.k.a. Kegel exercise) or surgery with a MUSling and assessed their subjective outcomes at 12 months post-randomization. Surgeons had the option of performing either a TVT or a TVT-O (a breakdown of results between the two types of surgery was not provided in the article). Women who were randomized to physiotherapy were more than 4 times as likely to cross over to the alternate treatment (i.e. surgery) than those in the surgery arm. This meant that 49% percent of the women assigned to physiotherapy opted to undergo surgery before the one-

year assessment. These women were still counted as being in the physiotherapy group at one-year evaluation. Despite the fact that almost one half of the women in the "physiotherapy" group ultimately had surgery prior to 12-month evaluation, the "surgery" group still had better outcomes. The rate of subjective (i.e. patient-derived) cure in the TVT group was 85% but only 53% in the physiotherapy group. It is highly likely that this difference would have been much more pronounced if women in the physiotherapy group had not been allowed to crossover prior to 12-month evaluation.

TVT is clearly superior to expectant management and physiotherapy in curing stress urinary incontinence.

TVT: Randomized Clinical Trials Comparing TVT to Non-sling Intervention

Surgical intervention for the treatment of SUI can be categorized in many ways. One of the most basic ways to dichotomize treatment options is based on the materials used. The first group of procedures is often referred to as a "suture-based repair" in which only sutures are used to stitch on part of the patient's body to another (the two major types are endopelvic fascia plication and suture colposuspension - including the Burch and the MMK procedure). The second group is "sling" surgery, in which a strip of material – sometimes biologic, sometimes synthetic – is used to support the urethra/bladder neck. This section of the report will focus on the randomized trials used to compare the synthetic TVT sling to suture-based repairs.

The suture-based repair with the longest history behind it is the endopelvic fascia plication. These procedures were first described by Kelly and Kennedy in the early 1900's, and since that time this surgery has often been referred to as the "Kelly" or "Kelly-Kennedy" plication. Performance of this procedure became much less common later in the twentieth century as other surgeries with more durable results came into vogue. Nonetheless, this procedure continues to be studied. The only RCT comparing endopelvic fascia plication to sling surgery was published in 2004. In this study, Meschia et al randomized women undergoing transvaginal surgery for the treatment of genital prolapse and occult SUI to undergo either an endopelvic fascia plication or a TVT sling (Meschia 2004).

Fifty women were randomized and peri-operative and long-term outcomes were measured. There were no differences in blood loss, surgical complication, or delayed voiding. At two-year follow-up both subjective (96% vs 64%) and objective (92% vs 56%) continence rates were higher after TVT versus suture plication. There were no differences in rates of urinary retention or de novo urge incontinence between the groups at follow-up. Based on this and other data the American College of Obstetrics and Gynecology (ACOG 2007) published a Practice Bulletin that states, "For women with positive prolapse reduction stress test results who are planning vaginal prolapse repair, TVT midurethral sling (rather than suburethral fascial plication) appears to offer better prevention from postoperative stress incontinence."

The procedure that largely supplanted the Kelly plication in the second half of the twentieth century was the colposuspension. There are two basic forms of the colposuspension: the MMK and the Burch procedure. The MMK procedure involves suturing the periurethral tissue at the level of the bladder neck to the posterior aspect of the pubic bone. In the Burch, the tissue is instead sutured to Cooper's ligament which runs along the top of the pubic bone. The

other major form of suture suspension surgery is known as the "needle-suspension". Due to poor outcomes these procedures were rarely performed after the late 1990's and therefor there are no RCT's comparing these procedures to TVT or other sling surgeries.

The colposuspension procedure has traditionally been performed through a relatively long transverse abdominal incision. This type of surgery is referred to as "open" abdominal surgery, to distinguish it from laparoscopic surgery in which multiple, very small incisions are used and visualization is achieved with a 5-10mm scope connected to a camera and displayed on a video monitor. The results of the first two RCT's to compare TVT to open colposuspension were published in 2002. Liapis et al (2002) reported on 71 women who were randomized to undergo either TVT or an open Burch colposuspension. This study found that the operative time was 3 times longer for the Burch, and the severity and duration of postoperative pain for TVT was much less than for the Burch. The time needed to return to normal activities was over twice as long for the Burch. All these peri-operative benefits did not come at the expense of efficacy; cure and improved rate for TVT was 91% and 92% for Burch at two years of follow-up.

A much larger study of TVT versus colposuspension was published the same year (Ward 2002). In this multi-center RCT patients in the colposuspension arm could receive either a Burch or a MMK colposuspension depending on what was the standard procedure at each given site. Randomization resulted in 175 women allocated to the TVT arm and 169 allocated to the colposuspension arm. In this initial publication, the women were followed for six months post-operatively. Outcomes at that time revealed a 66% cure rate in the TVT group and 57% in the colposuspension group. As with the Liapis RCT, the operative time, hospital stay, and return to normal activity were significantly shorter in the TVT patients. As expected, the rate of bladder perforation with the TVT needle was higher in the TVT group, but there were no long-term

sequelae associated with this perforation. Postoperative complications were more frequent in the colposuspension group including delayed return of bladder function/emptying, wound infection, fever, deep vein thrombosis, incisional hernia, and urinary tract infections.

When this same group of women was reassessed at two years post-operatively, higher cure rates were again seen in the TVT group, and the 12% greater cure rate seen in this intention-to-treat-analysis was shown to be statistically significant (Ward 2004). By the five-year follow-up only 35% of the originally randomized patients were available for follow-up and there was no longer a statistically significant difference in cure rates, but there was a notably higher rate of other pelvic floor dysfunction noted in the colposuspension group. The women in this arm of the study were more likely to develop pelvic organ prolapse – namely enterocele and rectocele – than in the TVT arm. Rates of surgery to correct pelvic organ prolapse were 4 times higher in the colposuspension versus the TVT group after 5 years of follow-up. Eleven of the 169 (7%) women originally randomized to colposuspension subsequently underwent surgery for prolapse. During this same 5-year time period, only 3 of the original 175 (1.7%) women randomized to the TVT group presented with a vaginal mesh erosion. Another small RCT comparing TVT and open Burch was published in 2005 (Bai) and also had an autologous sling arm. As would be expected given the sample size – 33 Burch and 31 TVT - no difference in efficacy between these procedures was noted. No morbidity results were reported.

It is not surprising that studies comparing the transvaginally-placed TVT to the transabdominal "open" colposuspension show less perioperative morbidity in the TVT group. However, one could theorize that a laparoscopic approach to colposuspension would lessen the morbidity within that arm. It was with this is mind that doctors at the Cleveland Clinic decided to perform a RCT comparing laparoscopic Burch colposuspension to TVT. In the initial

publication on this trial, 72 women were randomized and followed for 2 years (Paraiso 2004). Unlike the large RCT of open colposuspension described above, however, patients in this trial also underwent concurrent prolapse repairs and the time of their incontinence surgery, making an assessment of peri-operative morbidity difficult. Nonetheless, overall operative time and operative time for the incontinence surgery alone, were significantly shorter in the TVT arm of the study. Furthermore, the laparoscopic Burch group reported significantly higher subjective failure rates than TVT and 6 times as many patients with objective, urodynamic evidence of persistent SUI (there was only one patient with post-operative urodynamic SUI in the TVT group).

The authors of this paper continued to follow these patients beyond these two years and subsequently published their findings at 4-8 years of follow-up (Jelovsek 2008). This study was underpowered (only 25 patients in the TVT and 28 patients in the Burch group had long-term follow-up) and thus a failure to find a difference between groups does not mean that no actual difference exists. And in fact, the authors did not find significant differences in cure rates between these small groups. However, as analysis of other long-term literature shows (see **TVT: Long-term Data** section below), the durability of the Burch seemed to be much poorer than TVT. Subjects in this RCT who received laparoscopic Burch developed recurrent urinary incontinence at a median time of 52 months as compared to more the 87 months in the TVT group.

Another recent RCT comparing TVT to Burch urethropexy with short and long-term follow-up (Trabuco 2016 & 2018) did show greater overall continence rates in the TVT group. And as Table 1 shows, the risk of adverse events such as pain, dyspareunia, and retention are favorable with TVT as compared to native tissue (suture-based) repairs.

Table 1. Outcomes from randomized trials comparing Prolene mesh sling (TVT) to native tissue (NT) repair procedures for stress urinary incontinence.

	Pain			**Dyspareunia**			**Retention***		
Study	TVT	NT	P	TVT	NT	P	TVT	NT	P
Liapis 2002	0%	78%	<.001	NL	NL	-	0%	8.6%	NL
Ward 2002	18%	16%	.09	21%	20%	.097	3%	13%	<.01
Persson 2002	5%	0%	NL	NL	NL	-	41%	8%	NL
Wang 2003	NL	NL	-	NL	NL	-	NL	NL	-
Meschia 2004	NL	NL	-	NL	NL	-	8%	8%	1.0
Paraiso 2004	NL	NL	-	NL	NL	-	15.2%	14.7%	.80
Bai 2005	NL	NL	-	NL	NL	-	12.9%	0%	NL
Trabuco 2016	NL	NL	-	NL	NL	-	0%	1.8%	NS
*Retention requiring longer hospitalization, catheterization, or surgery to correct.									

The overall conclusion from this comparative data is that TVT has either equal or higher cure rates than suture-based incontinence surgeries. Furthermore, when compared to colposuspension, TVT is associated with shorter operative time, shorter, hospital stays and less peri-operative morbidity.

TVT: Randomized Clinical Trials Comparing TVT to Other Slings

There are 4 basic categories of slings other than TVT: traditional pubovaginal sling (PVS), other retropubic midurethral slings, transobturator midurethral slings/"tapes" (TOT), and "mini"/single incision slings (SIS). This section of the report will focus on the RCT's that compared TVT to these 4 categories of other slings.

Traditional Pubovaginal Slings

The era of sling surgery for urinary incontinence in women began with the development of the traditional pubovaginal sling (PVS). Initially, the patient's own (autologous) tissue was used to create the sling; most commonly the sling material was harvested by the patient's rectus fascia. Later on other biologic materials were used such as tissue from human cadavers and from other species (xenografts) such as pigs (porcine) and cows (bovine). All of the RCT's comparing TVT to PVS used either autologous fascia or a porcine xenograft in the PVS arm of the study.

The first RCT to compare TVT to PVS was published in 2003. This British study randomized 142 patients to receive either TVT or PVS with a porcine (Pelvicol TM, Bard) graft (Arunkalaivanan 2003) and followed them at a minimum of 6 months (range 6-24 months).The authors note no significant differences in outcomes between groups but review of the complications shows that 8.1% of the PVS patients had urinary retention lasting up to 6 weeks, while only 1.5% of patients in the TVT group had this problem; and more than twice as many patients in the PVS group (5) required sling release when compared to the TVT group (2). When the inventers of the TVT were developing this technique, they theorized that one of the benefits of "tension-free" placement would be less post-operative voiding dysfunction than that which was seen with PVS. This early RCT seemed to bear this out. The investigators of this study

published a second article reporting on three-year follow-up of these patients (Abdel-Fattah 2004). Again they noticed no difference in incontinence cure between groups. While they theorized, as others did, that the "biologic" nature of the porcine xenograft might reduce the risk of erosion as compared to the synthetic graft used in TVT, this did not seem to be the case. They did not report any erosions in either group.

The first RCT to compare TVT to PVS using autologous rectus fascia was published in 2008 (Sharifiaghdas 2008). As with the above study of the Pelvicol PVS, no differences were noted in objective cure of SUI, but the rate of voiding dysfunction (TVT = 20%, PVS = 30%) was higher in the PVS group. Unlike xenograft slings, autologous fascial slings need to be harvested from the patient through a transabdominal "open" incision. The next RCT to compare TVT to autologous PVS in which no concomitant prolapse repairs were performed at the time of sling placement highlighted this difference (Amaro 2009). The mean operative time for the autologous PVS was over twice as long as that of TVT (70 vs 33 minutes, $p < 0.05$).

One other RCT compared TVT to autologous PVS. In this study 53 patients were randomized to receive either TVT (28) or PVS (25) in Egypt (Wadie 2005). Unlike the previously described study, some prolapse repairs were also performed during the surgery, so operative time was not compared. In this study, 6 month follow-up revealed one 1 patient in the PVS groups with de novo detrusor activity compared to none in the TVT group, and 7 in the PVS arm with wound pain compared to only 2 in the TVT arm. No differences in objective cure of SUI were noted between the groups at last follow-up (range 6-48 months). No urethral or vaginal sling erosions were noted in either arm of this RCT. Another study comparing these two procedures was published 5 years later; it is unclear if some of the same patients were reported on in both studies (Wadie 2010). The randomization of subject in the second publication is

suspect, because almost 2/3 of the patients were in the PVS arm. In a properly randomized study the assignment should be at or very close to 50/50%. In any event, no significant differences were noted between groups in this study.

The most recent RCT of TVT and PVS looked at the use of porcine xenograft (Pelvicol) and autologous fascia in the PVS arm of the study (Guerrero 2010). In this large, multicenter study 201 women were randomized into three groups. As was previously shown, the autologous PVS had significantly longer operative times than the Pelvicol and TVT procedures. What was somewhat surprising though was that not only was the hospital stay longer in the autologous group, but also in the Pelvicol group. Both those groups stayed an average of 4 days in the hospital compared to only 2 days in the TVT group. Lastly the rate of voiding dysfunction was higher in the autologous group. The percentage of women in this arm who had to perform intermittent self-catheterization postoperatively was 9.9%, compare to only 1/5% of the TVT group.

Other Retropubic Midurethral Slings

With the advent and great success of the TVT retropubic midurethral slings came a number of other brands of retropubic MUS's. Many of these brands were not compared to the "gold-standard" TVT with RCT's, but two were. The first to be compared to TVT was a multifilament "tape" known as the intravaginal slingplasty (IVS). The second was the suprapubic arch sling (SPARC). Two RCT's were published on IVS and three on SPARC. A fifth RCT compared TVT to both IVS and SPARC.

The first study was published in 2003 (Rechberger). In this investigation 100 women were randomized yielding 50 patients per arm. The rate of bladder perforation was 8% in the IVS group compared to 4% in the TVT group ($p = 0.34$). While the rate of immediate postoperative urinary retention was higher in the TVT group (20% vs 4%, $p = 0.02$). No statistically significant difference in success was noted between groups despite the fact that complete cure was noted in 88% of the TVT arm compared to 80% of the IVS arm. The time of observation during which success was determined ranged from 4 -18 months. No mention of mesh erosion/exposure is made in this manuscript. This is noteworthy in that the multifilament meshes are frequently considered to be more prone to erosion.

This concern is highlighted by the second RCT published comparing TVT to IVS (Meschia 2006). In this study 190 women were randomized and standardized evaluations were carried out at 2 years postoperatively. Subjective success was noted in 87% if the TVT arm and in 78% of the IVS arm. Objective cure rates were 85% and 72% respectively. While these rates, particularly the objective rate trended towards statistical significance ($P = 0.06$); they did not strictly meet that criteria. However, the rate of vaginal mesh erosion/infection did. While there were no mesh erosions in the TVT group, 9% of the IVS required removal of the tape for erosions $P = 0.009$). This was a highly significant statistical and clinical difference. This property of multifilamentous mesh slings is responsible for a near complete abandonment of the use of this type of material for reconstructive pelvic surgery; while monofilament, macroporous polypropylene mesh remains the gold standard material for this purpose.

Two RCT's comparing TVT to the SPARC procedure were published in 2005 and the third in 2006. Unlike the IVS, the material properties of these two slings are similar; they are both made of monofilament, macroporous polypropylene mesh. The main difference between

the procedures is that needles used to place the TVT mesh are driven from a suburethral vaginal incision up behind the pubic bone and exiting through suprapubic skin incisions, while the SPARC needles are driven from the suprapubic skin incision down to the vagina. This approach is commonly known as the "top down" approach. Both of the 2005 trials showed comparable success rates in curing SUI between the two sling types, but they varied in the complication rate. One trial showed a high bladder perforation rate in both arms: 24% of the SPARC's and 23% of the TVT's (Andonian 2005). However, the other study showed a substantially higher rate in the SPARC group, 12.9% vs 0%. While this difference did not meet statistical significance, the authors concluded that the difference was clinically significant.

In the 2006 RCT over 300 women were randomized to the two procedures (Lord). While the bladder perforation and the short-term objective cure rates, >97% in both groups, were comparable between the TVT and the SPARC, the subjective cure rate was significantly higher in the TVT group, 87.1% vs 76.5%, $P = 0.03$. Furthermore, the rate of acute urinary retention was lower in the TVT group, 0% vs 6.5%, P = 0.002. The authors concluded that the SPARC was more difficult to adjust correctly. There was also a trend towards a lower rate of vaginal mesh erosion in the TVT arm, 4.5% vs 10.5%, P = 0.08.

The 3-arm RCT comparing TVT to IVS and SPARC was published in 2005 (Lim). This large trial randomized 195 "blinded" patients to one of these three procedures. All three groups had relatively good success rates. However, the SPARC trended towards a lower objective cure rate and TVT had the best cure rate: the rates were 87.9%, 81.5%, and 72.4% for the TVT, IVS, and SPARC groups respectively ($P = 0.11$). Given the multi-filament nature of the IVS one would suspect that the rate of erosion would be greatest with the IVS, but surprisingly this distinction belonged to SPARC: with observed incidences of 3.3%, 1.7%, and 13.1% for TVT,

IVS, and SPARC ($P = 0.04$). Over 80% of these erosions required trimming under general anesthesia. The incidences of bladder perforation were generally low (1.6 – 6.6%) in all three groups and did not differ significantly between arms. However, there was a non-significant trend ($P = 0.11$) towards the more problematic complication of urethral injury in the SPARC procedure – with three in the SPARC group and none in the other two groups.

Transobturator Midurethral Slings

By far, the procedure most extensively compared to TVT, is the transobturator midurethral sling. Many of the RCT's compare TVT to the Gynecare/Ethicon brand of transobturator sling known as the Tension-free Vaginal Tape – Obturator (TVT-O). The TVT-O sling is placed by starting at a suburethral vaginal incision and then passing a helical trocar laterally towards the obturator space. This has come to be known as an "inside-out" transobturator sling. To the best of my knowledge the Gynecare/Ethicon TVT-O is the only obturator sling studied in an RCT that utilizes the "inside-out" approach. However, there are also quite of few RCT's comparing TVT to transobturator slings in which the trocar is passed from a groin incision, through the obturator space and exiting through a suburethral vaginal incision, the so-called "outside-in" approach. These types of obturator slings are often collectively referred to as TOT (transobturator tapes), and this is the term I will use in this section of my report when referring them. Multiple device companies have marketed various outside-in approach TOT slings. I will focus first on the TVT-O trials and then finish with other TOT's.

TVT vs TVT-O

The first RCT's comparing the traditional retropubic TVT to the TVT-O were published in the mid- to late-2000's. Between 2006-2011, ten separate studies were published in which women were randomized to receive either TVT or TVT-O. The first study by Liapis et al (2006) investigated the results of 91 women with SUI, 89 of which were available for follow-up at one year postoperatively. In this study the mean operative time was shorter in the TVT-O group by approximately 9 minutes, but the length of stay was comparable. Likewise, the objective and subjective cure rates were very similar between groups. The authors' concluded that short-term outcomes with the TVT-O were "comparable to the classic TVT."

In 2007, three RCT's comparing these two slings were published. While two of these studies were carried out in Italy, different investigators and patients were involved in each. The first, like the 2006 study, was relatively small (n = 72) and followed patients for one year (Zullo 2007). As with the previous study, the operative times of the TVT-O were shorter than the TVT; but otherwise there were no significant intra-operative outcomes between groups. One-year outcomes were also comparable, averaging approximately 90% success. The second 2007 study was much larger (Meschia). In this study 231 women were randomized and followed for a median of 6 months. While 4% of the TVT patients had intra-operative bladder perforations compared to none in the TVT-O group, 5% of the TVT-O patients complained of thigh pain during their post-operative course. Subjective and objective cure rates were almost identical between groups, again averaging about 90%. Both procedures showed a highly significant improvement in incontinence-related quality of life outcomes. The third RCT published that

year came out of Finland (Laurikainen 2007). This study compared outcomes between 267 patients at short-term follow-up. No significant differences in objective or subjective cure rates were noted in this publication. These authors continued their follow-up of these patients for (as of the drafting of this report) for five years (2014). They found similar efficacy between the tow groups at this long-term follow-up. Treatment satisfaction in both groups remained >90% at five years.

The one RCT published in 2008 stratified 208 patients according to the severity of their SUI (Araco 2008). In this study, the operative times and postoperative pain levels were less with TVT-O than TVT. The cure rate in the patients with mild SUI was comparable between the sling types, but in patients with more severe incontinence, those who received TVT had a higher cure rate.

Three RCT's were published in 2009. The first (from Lithuania) followed 264 patients for 12 months (Aniuliene 2009). Surgical time was shorter in the TVT-O group, which also had fewer complications. But the effectiveness was similar and excellent in both groups. The second (from Turkey) followed 164 patients for 12 months as well, and found similar cure rates between groups (Karateke 2009). The last (from China, n = 315) looked at outcomes at 6, 12, 24, and 36 months (Wang W 2009). The slings had comparable success at curing incontinence. The operative time was shorter, but the postoperative groin/thigh pain was higher for TVT-O.

Two RCT's were published in 2010. One study out of France followed their patients for 2 years (Deffieux 2010). Cure rate and satisfaction rates were similar in the 149 patients randomized to either TVT or TVT-O in the study. The second RCT that year (out of the Czech

Republic) of 300 women, again, noted shorter operative times in the TVT-O group, but otherwise comparable objective and subjective cure rates (Krofta 2010).

These ten unique studies - in which every patient was randomized to either the Gynecare TVT or TVT-O - contained over 2000 women (total n = 2061). To the best of my knowledge, all ten of these RCT's showed a very low rate of sling erosion/exposure, and there were no significant differences in the erosion rates between the TVT and TVT-O.

TVT vs Other Transobturator Midurethral Slings (TOT)

There have been at least 7 studies in which TVT was randomized either to a non-Gynecare transobturator sling or to a combination of TVT-O and other TOT's. The first two large RCT's comparing TVT to a non-Gynecare TOT were published in 2008. One looked at a population with routine SUI whereas the other looked at a subpopulation of women with a more severe form of SUI known as intrinsic sphincter deficiency (ISD). The first compared TVT to a TOT (Monarc) marketed by American Medical Systems which funded the study through a research grant (Barber 2008). In this study 170 women were randomized, underwent surgery, and then were evaluated at a mean follow-up of 18 months after sling placement. While bladder perforations occurred more frequently in the TVT arm, the overall incidence of perioperative complications was similar. The authors concluded that the TOT was not inferior to TVT. The second trial also compared TVT to Monarc, but in this study the 164 women who were randomized had a more severe form of SUI known as ISD (Schierlitz 2008). Six months after surgery, urodynamic testing was performed and showed that 45% of the TOT group had recurrent urodynamic SUI compared to only 21% of the TVT group (P=.004). Nine in the TOT arm chose to have repeat surgery for SUI, while none of the patients in the TVT arm chose to do

so. The authors therefor concluded that, "TVT is a more effective operation than the transobturator tape sling in women with urodynamic (SUI) and (ISD)." Three-year follow-up of these same patients confirmed the short-term findings (Schierlitz 2012).

An Asian RCT of patients with SUI (not limited to just patients with ISD) with or without POP assigned study patients to receive either TVT or TOT and followed them for one year (Wang 2010). The authors of this study concluded that there were no significant differences in subjective and objective cure rates between groups. They did, however, note that in patients who did not have concomitant POP surgery, the operative times for the TOT patients was shorter.

The largest randomized comparison of TVT to transobturator slings was published in 2010 in the New England Journal of Medicine (Richter 2010). In this RCT, 597 women were assigned to receive either TVT or transobturator sling (it was at the surgeons discretion whether this sling was a Gynecare TVT-O or an AMS Monarc TOT) and 565 (94.6% returned for 12-month postoperative assessment. Objective success (80.8%vs 77.7%) and subjective success (62.2% vs 55.8%) were comparable between groups. The rates of voiding dysfunction requiring surgery were higher in the TVT group (2.7% vs 0%, P=.004), but adverse neurologic symptoms were worse in the TOT group (4.0% vs 9.4%, P=.01). There were no significant differences between groups in postoperative urge UI, satisfaction with the results of the procedure, or quality of life. A two-year follow-up of these patients still showed no significant change in patient satisfaction which remained high, but equivalence of objective success was no longer met and favored TVT over TOT (77.3% vs 72.3%) (Albo 2012).

Two European RCT's comparing TVT to transobturator slings were published soon after the U.S. study. While not as large as the U.S. trial the results were relatively similar. The first,

published in 2011, randomized 193 women in the United Kingdom to receive either TVT or TOT (AMS Monarc) and followed them for 12 months (Freeman 2011). The primary outcome measure was subjective cure and in regards to this outcome the authors concluded that the TOT was not inferior to TVT (63.4% vs 65.5% respectively). There was a higher (albeit non-significant) rate of reported groin pain in the TOT group, but no difference on impact in sexual function between groups. The second study, published in 2012, randomized 160 Swiss women in a 2:1:1 ratio to TVT, outside-in TOT (AMS Monarc), or inside-out TVT-O (Gynecare) and followed them for 12 months (Scheiner 2012). Again, continence rates and voiding function following all three methods of sling were comparable. However, enrollment was halted early when interim analysis noted a higher rate of female sexual dysfunction (P=.011) and vaginal tape exposures (P=.028) were noted in the outside-in TOT (AMS Monarc), when compared to the other two groups.

Mini/Single-Incision Slings

Single-incision (a.k.a. mini-slings) slings (SIS) were first compared in a randomized fashion to the full-length, retropubic TVT in 2010. Investigators in Egypt randomized 60 women to receive treatment with either TVT or TVT-Secur (Abdelwahab 2010). The authors found that operative time and intra-operative morbidity were lower in the TVT-Secur group. But there was no difference in voiding or continence after 9 months of follow-up. Longer-term follow-up was not presented.

The following year two randomized trials involving TVT and TVT-Secur were published. The first randomized 126 women to one of these two procedures but again only reported short-

term follow-up (Hamer 2011) in this publication. At 2 months of follow-up the authors noted significantly superior subjective cure rates in the TVT group, 92% vs 72% (p=0.01). Surgical time was shorter (22 vs 13 minutes) in the TVT-Secur group, but the number of major complications was higher (0 vs 3). No significant differences were found between groups regarding perioperative bleeding, hospital stay, urge symptoms, or postoperative urinary tract infections. The other RCT that year comparing TVT to TVT-Secur also included a transobturator arm (TVT-O) as well (Wang 2011). A total of 102 women were randomized to one of these three arms. As with the Hamer study, cure rates in the mini-sling arm were lower than TVT. At one year follow-up, complications were not statistically different between TVT and TVT-Secur.

The largest RCT was published in 2012 and again compared TVT to the TVT-Secur mini-sling (Barber 2012). This was a multi-center, noninferiority trial in which 263 women were randomized (sham suprapubic incisions were used in the mini-sling arm to "blind" subjects to group membership). Bladder injury, need to be discharged home with a catheter, and days 1-3 postoperative pain rates were significantly lower in the mini-sling arm. However, the authors concluded that while there were similar subjective cure rates at one year after surgery, postoperative incontinence severity was greater in the mini-sling arm (this was due primarily to a higher proportion of participants with "sever" incontinence postoperatively – 16% vs 5%, p=0.03).

In 2013 Hamer et al published the longer-term outcomes from their original 2011 manuscript (Hamer 2013). The vast majority of the originally randomized women were available for follow-up at a median of 12-13 months. As with the short-term evaluation, the subjective cure for TVT was greater than the mini-sling (98% vs 80%, p+0.03). Objective cure

rates were also noted to be superior in the TVT arm (94% vs 71%, p=0.03). No differences in complications past the initial short-term (2 month) follow-up were noted.

The overall conclusion from this comparative data is that TVT has either equal or higher cure rates than other sling surgeries. Furthermore, when compared to traditional pubovaginal sling, TVT is associated with shorter operative time, less blood loss, shorter hospital stays, and less postoperative voiding dysfunction. TVT carries a lower risk of vaginal erosion than other retropubic synthetic midurethral slings. When compared to transobturator slings, TVT is associated with a lower risk of groin pain and in some studies a lower rate of sling erosion. Furthermore, TVT appears to have greater success in curing SUI in patients with intrinsic sphincter deficiency. Finally, TVT results in greater cure rates than mini/single-incision slings.

Summary of Conclusions of RCT Data

There is no other treatment (surgical or non-surgical) for stress urinary incontinence in women that has been more studied in randomized clinical trials than TVT. All the cumulative data from these studies demonstrates that the efficacy of TVT is either equal or superior to all other options in the treatment of SUI in women.

TVT: Long-term Data

While many other types of surgeries for SUI have been studied in RCT's, no other surgery for SUI has more long-term data than the TVT. This is particularly important in the case of TVT for two reasons both relating to the permanent nature of the sling material. Unlike native tissue repairs or other biologic or absorbable synthetic grafts which can theoretically lose effectiveness as the repair or graft suffers degradation, the graft used in TVT is non-absorbable. One would hope that this means that the effectiveness demonstrated in short-term studies should not diminish much over longer periods of time, but only long-term studies can tell us that for sure. Likewise, long-term studies can potentially reassure us that the graft-related complications seen in short-term studies do not worsen significantly and that new, unforeseen complications do not develop over long periods of time.

One of the first long-term studies of TVT came out of Greece (Liapis 2008). This investigation is a prospective assessment of the efficacy and complications associated with the use of TVT at 5- and 7-year follow-up. Sixty-five women were included in this study that showed an objective cure rate of 83% at five years that dropped minimally to 80% at seven years. Rates of de novo detrusor overactivity were also relatively stable, noted in 9.4% and 11.4% of patients at the 5 & 7 year follow-up respectively. The authors concluded that the TVT operation was effective and safe in women with SUI in long-term follow-up.

There are at least 7 distinct cohorts of patients that have been followed for ten or more years following TVT and reported on by distinct author groups. These investigations have yielded at least nine publications in peer-reviewed journals. While this may not seem particularly remarkable to someone not directly involved in the field of FPM&RS, to those within the specialty, it is indeed remarkable. No other procedure used to treat not only incontinence of any type, but even pelvic organ prolapse, has such extensive long-term data to support its use.

In 2010 Olsson et al published a retrospective review of 147 women who underwent TVT between 1994 and 1997. Range of follow-up ranged from 10-13 (average 11.5) years and 84% of the subjects were evaluated (of those not evaluated were 19 patients who had died since the procedure and 4 who were disabled). The objective cure rate was 84% and satisfaction rate was high at 94%. Three women (1.2%) needed sling revision for voiding dysfunction. The authors did not observe any late tape rejection.

In 2011 Aigmueller et al published a retrospective review of 210 patients who underwent the TVT procedure between the years of 1999 and 2001 at two centers in Austria. One hundred forty patients were available for follow-up (average length of follow-up was ten years), and objective cure was noted in 84% of patients. Six of the original 210 patients (2.9%) underwent sling revision for voiding dysfunction and 2 underwent revision for mesh erosion. One additional patient had a minor vaginal mesh exposure at follow-up that did not require surgical intervention; for a total mesh erosion/exposure rate of 1.4% (2.1% of those available for follow-up).

Also in 2011, Groutz et al also reported on a retrospective series of TVT patients with ten-year follow-up. This was a structured telephone interview study of 60 Israeli women. Fifty-two (87%) of the women were available for ten-year follow-up. 77% of the women felt their condition was either cured or improved (it should be noted that over half of the patients had concomitant urge incontinence and TVT is not intended to cure this condition, potentially accounting for why some of the women felt their "condition" was not cured). Only 4% of women underwent a second surgery for incontinence during the ten years of follow-up. The authors concluded that TVT "has stood the test of time, and is now considered the criterion standard against which other procedures should be compared."

In 2012, a Finish group reported on a series of 191 patients who underwent TVT (Heinonen 2012). Over 70% of these patients were evaluated after a mean of 10.5 years after surgery. The objective and subjective cure rates were 90% and 78% respectively. Only three had late-onset adverse events. The same year, an Italian group also reported the results of a prospective case series of 63 women ten years after undergoing TVT (Serati 2012). This series of patients were also evaluated at 1,3, and 5 years post-op and cure rates were stable throughout the whole study period. Only 5 patients were no available for follow-up (3 had died and 2 were lost to follow-up). The objective and subjective cure rates were 93% and 90% respectively. Other than intraoperative bladder perforation in two on the cases, no other complications occurred. There were no cases of sling revision, de novo dyspareunia, vaginal, bladder or urethral erosion in the 58 patients available for 10-year follow-up.

In 2013, a Norwegian group reported on a group of 603 women who underwent the TVT surgery between 1998 and 2000 (Svenningsen 2013). At the time of data collection 542 were alive and of those 483 (89%) were available for follow-up at a median duration of over ten years.

Objective and subjective cure rate were 89.9% and 76.1% respectively. Over 82% of patients stated that they were "very satisfied" with their surgery. Only 2.3% of the women had undergone repeat surgery for SUI. Only one case of mesh exposure (asymptomatic) was noted at long term follow-up. Three additional cases had been previously diagnosed and treated, for a overall exposure rate of 0.8% for the whole ten year period. There was no significant change in objective cure rate when comparing one-year to ten-year outcomes (90.2 % vs 89.9%, P=0.86).

The most remarkable long-term series of TVT patients comes, not surprisingly, from the area of the world in which it was invented, Scandinavia. Nilsson et al (2001, 2004, 2008, and 2013) followed a series of Swedish and Finnish patients and reported on their outcomes at 5, 7, 11, and 17 years after initial implantation. This cohort of 90 women was followed prospectively with objective and subjective outcomes obtained at regular intervals. The objective cure rate at 17 years of follow-up was 91% and this represented no decline in cure between the 5 and the 17 year evaluation. The subjective perception of either cure or improvement was 87%, which represented a slight decline from the 11 year follow-up. In the majority of those who felt their continence status was not improved, their leakage was from urgency incontinence and not a late recurrence of SUI. Only one patient underwent a repeat surgery for SUI, and that was done 15 years after the original TVT. The authors also report some other important outcomes. They concluded that there was no significant shrinkage of the TVT mesh over long periods of time, because the residual amount of urine in the patients' bladders after voiding was within normal limits in all but two patients. These two patients had other conditions that were the most likely cause of their elevated residuals: Parkinson's Disease and grade III cystocele. On examination only one patient had a vaginal mesh exposure. It was not symptomatic and she was highly satisfied with her surgery. She was 69 years old, had vaginal atrophy, and her exposure was

treated medically with vaginal estrogen. This exposure found at her 17–year visit was not seen at her 7-year visit (she did not come for exam at 11-years). No other adverse effects or reactions to the mesh material were detected on the women who were examined. No visceral (urethral or bladder) erosions were reported in this cohort of women. Very recently a second study with 17 year follow-up was published from a center in Greece that showed similar high rates of long-term cure of SUI and a very low complication rate (Bakas 2018). A third study with 17 year follow-up was also recently published that was prospectively conducted in two centers (one in Switzerland and one in Italy) that showed similar high rates of long-term cure of SUI (91.4% objective cure and 89.1% subjective cure) that did not deteriorate over time and a very low complication rate (Braga 2018). No vaginal, bladder or urethral exposure/erosion or de novo dyspareunia were reported and no patient underwent TVT release or resection.

There is much less long-term data on other types of anti-stress incontinence surgery. However there is one RCT (Richter 2012) comparing Burch colposuspension to pubovaginal sling (in which autologous rectus fascia was used for the sling material) – the SISTEr trial. The cure rates for these procedures at 7 years of follow-up were much lower than the rates we see for TVT at 17 years. The cure rate for autologous rectus fascia sling at 7-year follow-up was 27% and only 13% in the Burch group. It is challenging to compare cure rates between two different studies and one could argue that the criteria for cure was more strict in the SISTEr trial than in the long term series of TVT. However, the same criteria were used to assess cure at 2-year and 7-year follow-up in the SISTEr trial and it is clear that there is a steep drop-off in success in both procedures. The 2-year cure rate of sling goes from 52% down to 27% at 7-years and in the Burch it goes from 42% down to 13%. This shows the lack of durability in these procedures. The same is not seen in long-term studies of TVT in which the same definition of cure is used at

different lengths of follow-up. In these studies, there is very little drop in cure rates of TVT after 2 years.

There is also one other long-term comparative study comparing two anti-incontinence procedures. This is not a randomized trial, but rather a retrospective cohort study comparing 12-year outcomes in patients either underwent TVT placement or Burch colposuspension (Holdo 2017). In this study, the authors noted a significantly higher recurrence rate of SUI in patients who underwent the Burch procedure. They noted no differences in rates of perioperative and late complications. At 12 years post-op the authors found a significant increase in rates of repeat surgery for incontinence and prolapse in women after Burch as compared to TVT.

Summary of Conclusions of Long-Term Data

The overall conclusion of all these long-term studies is that when the TVT is performed with proper technique, the risk of tape/mesh-related problems is very small and the rates of long-term cure are high.

V. TVT – O: COMPARATIVE AND LONG-TERM DATA

While the original retropubic TVT is the most studied sling procedure in history, the TVT-O is arguably the second most studied sling of all time. Again given the extensive nature of the data, I will limit my discussion of the literature to RCT's not already covered in this report, prospective cohort studies, and long-term studies of TVT-O. Much of this literature has already been covered earlier in this document, particularly the studies comparing TVT-O to the original retropubic TVT

TVT-O: Randomized Clinical Trials

There have been at least ten RCT's directly comparing TVT-O to the original retropubic TVT. Since these were reviewed earlier in my report (begun on page 41), I will not go over these particular studies again. Instead, I will cover the RCT's comparing TVT-O to non-surgical intervention, to non-sling surgeries for SUI, and to other slings (again excluding studies comparing TVT-O to TVT).

TVT-O: Randomized Clinical Trials Comparing TVT-O to Non-Surgical Intervention

There has been one RCT conducted that compares non-surgical intervention for SUI to TVT-O (Labrie 2013). This Dutch study published in the New England Journal of Medicine randomized 460 women to receive either pelvic floor physical therapy (physiotherapy, a.k.a. Kegel exercise) or surgery with a midurethral-sling and assessed their subjective outcomes at 12 months post-randomization. Surgeons had the option of performing either a TVT or a TVT-O (a

breakdown of results between the two types of surgery was not provided in the article). Women who were randomized to physiotherapy were more than 4 times as likely to cross over to the alternate treatment (i.e. surgery) than those in the surgery arm. This meant that 49% percent of the women assigned to physiotherapy opted to undergo surgery before the one-year assessment. These women were still counted as being in the physiotherapy group at one-year evaluation. Despite the fact that almost one half of the women in the "physiotherapy" group ultimately had surgery prior to 12-month evaluation, the "surgery" group still had better outcomes. The rate of subjective (i.e. patient-derived) cure in the TVT/TVT-O group was 85% but only 53% in the physiotherapy group. It is highly likely that this difference would have been much more pronounced if women in the physiotherapy group had not been allowed to crossover prior to 12-month evaluation.

TVT-O: Randomized Clinical Trials Comparing TVT-O to Non-Sling Surgical Intervention

I could find no randomized trials comparing TVT-O to surgical interventions other than slings, such as a Burch colposuspension.

TVT-O: Randomized Clinical Trials Comparing TVT-O to Other Slings

Studies comparing TVT-O to other slings (other than the original retropubic TVT) fall into two basic categories: those comparing TVT-O to other obturator slings and those comparing TVT-O to single-incision slings. I will start by reviewing the data comparing TVT-O to other obturator slings.

The only studies comparing TVT-O to other obturator slings involve the comparison of TVT-O to "outside-in" obturator slings that I will refer to as TOT's (short for Trans-Obturator Tapes). There are at least 5 published RCT's in which patients were randomized to TVT-O or TOT (in two of the studies there was a third arm; one study also randomized to a single-incision sling and one to a retropubic sling as well).

In the first study published, 120 women were randomized to either TVT-O or the Monarc TOT (American Medical Systems, Minneapolis, MN, USA) and followed for twelve months; 114 were available for follow-up at 12 months (Liapis 2008). In this study the subjective, objective and improvement rates were statistically comparable between both procedures. The subjective cure or improved rate was 93% for TVT-O and 88.5% for Monarc. However there was one urethral injury, and this was in the TOT group. This is a very uncommon complication of a MUS and is therefor notable. There were no mesh exposures in either group.

In the next study, there were three possible arms that the 187 women within the trial could be randomized: retropubic TVT, TVT-O, or TOT (Chen 2010). There was no statistical difference in cure rates between TVT-O and TOT, 92.3% and 91.1% respectively. Complication rates were comparable between the TVT-O and TOT groups and both were lower than in the TVT group. The biggest difference being that there were no bladder injuries with both types of obturator procedures, whereas the rate for the retropubic TVT was 5.3%.

The other study in which three randomized groups were compared also looked at the same three procedures as the above study. In this investigation, voiding function was the primary outcome; specifically "uroflow" rates were compared (Scheiner 2012). Both obturator arms contained 40 patients and outcomes were assessed at 12 months post-op. There was no

significant difference in maximum flow rates in all three groups and continence rates were also comparable (all > or = 89%). However, mesh exposure rates and de novo sexual dysfunction rates were significantly higher in the TOT group when compared to the TVT-O group, at 10% vs 0% (P=0.028) and 17% vs 0% (P=0.011) respectively.

Two of the RCT's followed patients out for at least 3 years and both of these studies were published in 2012 (Park 2012, Abdel-fattah 2012). In the first study, 74 patients were randomized to either the Monarc TOT or TVT-O (Park 2012). Subjects were followed for an average of 39 months. Cure rates were comparable between groups 85.7% and 84.6% respectively (P=0.348). Likewise, patient satisfaction rates were similar as well, with 82.8% versus 82.1% either "very satisfied" or "satisfied" with their outcomes (P=0.652 and 0.734). Difficulty with voiding, dyspareunia, and inner thigh pain were less than 3% in both groups, with no significant difference between groups. There were no bladder or urethral injuries in either group. In the second study, 341 were randomized to either TOT-Aris (Coloplast Corp., Minneapolis, MN, USA) or TVT-O. Of these, 299 were available for post-operative follow-up at one year (Abdel-fattah 2010), and 238 were available at three years (Abdel-fattah 2012). At one year, there was no difference between groups in terms of patient-reported success (77.6% vs 81.2%, P=0.54) and objective cure (88% vs 94%, P=0.157). At three years, there were still no differences noted between groups with success rates (defined as very much/much improved) of 72.3% and 73.8% respectively (P=0.796). In this study, the authors also looked at the patients for even longer follow-up, with a median time of 9 years (Karmakar 2017). There was no difference between groups at this time frame (P=0.76) and no significant reduction of success rates overall when compared to outcomes at three years.

The other type of sling that sling that has been compared to TVT-O in randomized trials is the single-incision sling (SIS). There are at least six randomized trials comparing TVT-O to SIS's. Most of these compare TVT-O to the TVT-Secur (Gynecare, a division of Ethicon Inc., Somerville, NJ, USA) procedure, but one also compares it to MiniArc (American Medical Systems, Minnetonka, MD, USA). Both the TVT-Secur and the MiniArc are SIS's manufactured by different companies.

The only RCT to compare TVT-O to two different types of SIS was published in 2011 (Oliveira 2011). In this study ninety consecutive patients were enrolled in a randomized to either TVT-O, TVT-Secur, or MiniArc and then followed for 12 months. Cure was defined as the absence of urine leakage, no pad use, and a negative cough test. Cure rates were 83%, 67%, and 87% respectively and improvement rates were 10%, 13%, and 7%. Complication rates were 30%, 17%, and 20%. The authors concluded that TVT-O and MiniArc had similar cure and improvement rates, but that TVT-Secur might not be as effective as the other two approaches.

The other five studies compare TVT-O to TVT-Secur alone or in combination with the retropubic TVT. The first of these was an Italian RCT of 84 women with SUI (Tommaselli 2010). In this study the authors followed these women for 12 months. They found that the cure rate was comparable between the groups at 81.6% for TVT-O and 83.8% for TVT-Secur. No intraoperative complications were observed in either group. Likewise, there was no statistically significant difference in the rate of postoperative complications between groups. The next study was a multicenter Dutch and Belgian study comparing TVT-O and TVT-Secur (Hinoul 2011). Nearly 200 women were randomized in this one-year trial. While the SIS group noted less pain within the first 2 postoperative weeks in the SIS arm of the study, the TVT-O groups had superior one-year objective cure rate (P=0.002). That same year a group of Chinese surgeons

performed a RCT in which 102 women were randomized to TVT-O, TVT-Secur, or the retropubic TVT (Wang 2011). While the cure rates were similar between TVT-O and TVT, the cure rate for the SIS was also lower in this study. A multi-center U.S. study of TVT-O and TVT-Secur published the following year included a total of 87 women (Hota 2012). While the authors noted similar improvements in quality-of-life measures after each procedure, the overall risk of objective SUI was lower in the TVT-O arm of the study. The final RCT was performed in the Czech Republic and followed patients for two years (Masata 2012). In this RCT, 197 women were randomized to receive either TVT-O or TVT-Secur. As with the majority of the one-year studies, the cure rate in the TVT-O arm of the study at two years was significantly higher in the TVT-O group.

TVT-O: Prospective Non-Randomized Studies of TVT-O

There are two high-quality, non-randomized, prospective studies comparing the inside-out TVT-O to outside-in TOT slings. The first is a Korean study comparing the outcomes of 50 women who underwent TVT-O to those of 50 women undergoing a TOT (Dow Medics, Korea) (Lee 2008). At one-year the cure or improved rates were 96% in both groups. Subjective satisfaction rates were also comparable between groups. Finally, the percentage of patients within each group that would recommend the procedure to other patients was 96% for TVT-O and 90% for the TOT (P=0.22). Likewise, operative time, amount of intraoperative bleeding, thigh discomfort, and time to normal activity were not statistically significantly different between groups. There were no serious perioperative complications (i.e. bladder perforation, infection, or significant nerve or vessel injury) in either group.

The other prospective cohort study compared 191 women who underwent either TVT-O or Monarc (American Medical Systems, Minneapolis, MN, USA) (Houwert 2009). As with the above noted randomized trials comparing TVT-O to Monarc, no difference was noted in cure rate between these two types of slings. Quality of life measures (including the "Incontinence Impact Questionnaire" and "Urinary Distress Inventory") showed significant improvement in both groups. The degree of improvement in these measures was not different between groups. Length of surgery (P=0.90) and blood loss (P=0.30) was also comparable between groups. Long-term (2-4 years) follow-up revealed 1 (1%) vaginal mesh erosion in the TVT-O group and 4 (5%) in the Monarc group (P=0.40). Also at this time period, there was one case of dyspareunia (1%) in the TVT-O group and zero in the Monarc (P=1.00); and zero cases of persisting thigh pain in the TVT-O group and 1 (1%) in the Monarc group (P=1.0).

Summary of Conclusions of Comparative TVT-O Data

Other than the original retropubic TVT, there is no other specific sling procedure that has been more researched in comparative studies than TVT-O. All the cumulative data from these studies demonstrates that the efficacy of TVT-O is either equal or superior to those other slings in the treatment of SUI in women. TVT-O also appears to be superior to pelvic floor physiotherapy for the treatment of SUI in women.

TVT-O: Long-term Data

There are numerous long-term studies of the TVT-O procedure. Not surprisingly, given the fact that it was developed years after the original retropubic TVT, there are fewer long-term studies than we find with TVT and the length of follow-up is not as extensive. Nonetheless, I will now review seven studies of TVT-O that look at patient outcomes at 2-, 3-, 4-, 5-, 7-, 9-, and 10-years post-surgery.

The first study was performed in Asia and followed 67 women with severe pre-operative SUI (SU 2009). The authors collected both objective and subjective data at a median follow-up of 24 months. They found an objective cure rate of 76.2%, a significant reduction of leakage on pad-weight testing, and a subjective cure (83.5%) or improved (14.9%) rate of 98.4%. Quality of life measures also showed significant improvement and only one (1.5%) mesh extrusion was noted over the length of the study. There were no major complications.

The next study looked at prospectively collected 3-year data of TVT-O as part of a RCT investigating women with mixed UI (Abdel-Fattah 2014). In this U.K. study 31 women completed 3-year follow-up. This study showed that not only were the overall success rates good, but that >50% of the patients reported cure of pre-operative urgency and urge incontinence in particular. The majority of patients also showed clinically significant improvements in quality of life as measured by the King's Health questionnaire.

Another European study looked at 4-year TVT-O outcomes in 74 patients who underwent sling placement alone and another 41 patients who had TVT-O with a concomitant anterior colporrhaphy (Liapis 2010). Pad testing revealed an objective cure rate of 82.4% with another

6.8% improved for the TVT-O-only patients and a very similar cure/improved rate (80.5%/7.4%) for those that had a concomitant anterior colporrhaphy.

In a Japanese 5-year prospective cohort study comparing TVT-O to an "outside-in" transobturator sling procedure, long-term cure rates similar to the above 4-year study were found (Cheung 2014). Eighty-nine women underwent TVT-O in this study and were seen in follow-up annually for a total of 5 years. Subjective cure was defined as women denying experiencing any urine loss on physical activity, and objective cure was defined as no urine leak with cough during urodynamic testing. Cure rates for the TVT-O were 84.1% and 82.5% respectively. Complication rates were low at by five-years out. Of note; cure rates, rates of de novo overactive bladder symptoms, and complication rates were comparable between the TVT-O and the outside-in sling groups.

Another long-term comparative study of these two approaches to transobturator sling placement conducted in Korea followed patients for 7-years (Chun 2014). In this study of 215 patients, 86 underwent TVT-O. After a median follow-up of 7.1 years the cure rate for TVT-O was 67%. The cure rate was noted to be higher in the outside-in groups, but this may be due to the fact that pre-operatively a greater number of the patients (>50%) in the TVT-O group had mixed UI. This type of confounding variable often found in observational studies is much less often found in randomized prospective trials.

The longest surgical outcome data of transobturator slings from a randomized trial comes from the E-TOT trial performed in the UK (Karmakar 2017). The primary outcome was patient-reported success rate, defined as "very much/much improved" on the Patient's Global Impression of Improvement scale. There was no difference noted in this outcome between the

two surgical approaches, with an overall success rate of 71.6% and another 14% reporting "improvement". Thus >85% of patients were improved from their pre-operative status at a median follow-up of 9.2 years. This 71.6% success rate at 9 years is clinically comparable to the rate (73.1%) noted at 3 years of follow-up in the same group of patients. Sling extrusion/erosion rate was 4.5% and less than 1.5% of patients required treatment for groin pain in this study.

Finally, the longest-term data we have to date on the TVT-O procedure includes two studies with 10 year follow up. The first comes out of Austria (Ulrich 2016). In this study 124 women underwent surgery. When the authors endeavored to follow-up with this group of patients ten years later, they found that 112 women were still alive. Of these women, half (55) were available for clinical examination and 71 (63%) completed questionnaires regarding their current state of continence. Objective cure was defined as a negative cough test at a standard bladder volume of 300 mls. The objective cure rate was noted to be 69%. Similarly 64% (45/71) of the women who completed validated questionnaires considered themselves subjectively cured. Three (5%) of patients had vaginal sling extrusion at the ten-year follow-up examination. In all 3 cases, the mesh extrusion was small and asymptomatic. The second comes out of Italy (Serati 2017). In this study 168 patients underwent surgery and at 10 year follow up 95% (n=160) were available for follow up. 155 of 160 patients (97%) declared themselves cured and 148 of 160 patients (92%) were objectively cured, without significant deterioration over time. Only two patients underwent a second incontinence procedure (a retropubic MUS). No patient required tape release or resection and no significant prolapse, vaginal, bladder, or urethral erosion were recorded. One patient noted persistent mild groin pain at 10 year follow up with a visual analog scale score of 2 of 10, not requiring analgesic treatment. Four of 92 sexually active patients (4.3%) noted dyspareunia at 10 years, when asked whether they feel pain during

intercourse. This issue is confounded by the aging of the patients and the background prevalence of dyspareunia in the female population which is frequently reported at more than 20%. In these cases, local estrogen was prescribed per the authors.

Summary of Conclusions of Long-Term TVT-O Data

The overall conclusion of these long-term studies is that the TVT-O procedure is associated with very low rates of tape/mesh-related complications and the rates of long-term cure are high.

VI. Systematic Reviews

There have been multiple systematic reviews of anti-SUI surgeries that have included a review of the data on midurethral slings; including TVT and TVT-O. When one analyzes these reviews it is clear that by far the two slings that are most referenced in these studies are the Gynecare TVT and TVT-O. These systematic reviews, which often include meta-analysis, confirm the conclusions that I have drawn in this report from my review of the peer-reviewed data. I will now briefly discuss the pertinent systematic reviews/meta-analyses.

A Cochrane Review of MUS (including TVT and other MUSlings) published in 2011 (Ogah) looked at 62 RCT's including over 7000 women, and concluded "synthetic suburethral slings are as effective as traditional suburethral slings, open retropubic colposuspension and laparoscopic colposuspension in the short-term but with less postoperative complications." The authors noted: Minimally invasive synthetic suburethral sling operations (TVT) appeared to be as effective as traditional suburethral slings [8 trials, n = 599, risk ratio (RR) 1.03, 95% confidence interval (CI) 0.94--1.13] but with shorter operating time and less postoperative voiding dysfunction and de novo urgency symptoms. Minimally invasive synthetic suburethral sling operations appeared to be as effective as open retropubic colposuspension (subjective cure rate at 12 months RR 0.96, 95% CI: 0.90--1.03; at 5 years RR 0.91, 95% CI: 0.74--1.12) with fewer perioperative complications, less postoperative voiding dysfunction, shorter operative time, and hospital stay but significantly more bladder perforations (6% vs. 1%, RR 4.24, 95% CI: 1.71--10.52). There was conflicting evidence about the effectiveness of minimally invasive synthetic suburethral sling operations compared to laparoscopic colposuspension in the short term (objective cure, RR 1.15, 95% CI: 1.06--1.24; subjective cure RR 1.11, 95% CI: 0.99--1.24). Minimally invasive synthetic suburethral sling operations had significantly less de novo

urgency and urgency incontinence, shorter operating time, hospital stay, and time to return to daily activities. A retropubic bottom-to-top route was more effective than top-to-bottom route (RR 1.10, 95% CI: 1.01--1.20; RR 1.06, 95% CI: 1.01--1.11) and incurred significantly less voiding dysfunction, bladder perforations, and tape erosions. Monofilament tapes (like TVT and TVT-O) had significantly higher objective cure rates (RR 1.15, 95% CI: 1.02--1.30) compared to multifilament tapes and fewer tape erosions (1.3% vs. 6% RR 0.25, 95% CI: 0.06--1.00). The obturator route was less favorable than the retropubic route in objective cure (84% vs. 88%; RR 0.96, 95% CI: 0.93--0.99; 17 trials, n = 2,434), although there was no difference in subjective cure rates. As with the other systematic reviews, the Gynecare TVT and TVT-O were the most commonly referenced procedures within this review.

A review by Schimpf et al looked at studies comparing all types of slings to other forms of anti-SUI surgeries (Schimpf 2014). In regards to the outcomes of midurethral synthetic slings (and again the Gynecare TVT and TVT-O represented the sling used in the vast majority of these studies) compared to the native tissue (i.e. Burch) procedures, they concluded that, "Midurethral slings may result in lower rates of perioperative adverse events such as blood loss, postoperative pain, operating room time, hospital stay, bowel injury, wound infection, and hematomas."

Tommaselli et al published medium-term and long-term outcomes of midurethral slings for SUI, and again the Gynecare TVT and TVT-O represented the sling used in the vast majority of these studies (Tommaselli 2015). In this review the retropubic-MUS (such as TVT) had similar objective cure rates (OR 1.15, 95 % CI 0.75 – 1.76) but higher subjective cure rates than

transobturator-MUS (OR 1.76, 95 % CI 1.08 – 2.86). No differences were observed between outside-in (TOT) and inside-out (TVT-O) and between transobturator, MUS, and minisling. Bladder injuries were more frequent (OR 7.01, 95 % CI 2.94 – 17.90) and vaginal erosions were less frequent for retropubic MUS (OR 0.24, 95 % CI 0.07 – 0.84). Vaginal injuries were more common with the outside-in TOT than with TVT-O (OR 7.96, 95 % CI 1.15 – 157.9). Pain-related complications were more common with transobturator MUS than with minimally invasive tapes (OR 8.75; 95 % CI 9.02 – 57.90).

The most recent Cochrane systematic review of midurethral slings (Ford 2015) concludes that, "Mid-urethral sling operations have been the most extensively researched surgical treatment for stress urinary incontinence (SUI) in women and have a good safety profile. Irrespective of the routes traversed, they are highly effective in the short and medium term, and accruing evidence demonstrates their effectiveness in the long term. This review illustrates their positive impact on improving the quality of life of women with SUI." As noted earlier, the Gynecare TVT and TVT-O represented the slings studied in the majority of these trials included in this systematic review.

A systematic review of surgical treatments of female stress urinary incontinence showed similar efficacy between outside-in TOT and TVT-O techniques (Fusco 2017). However, when the authors performed a meta-analysis of complications, the inside-out technique used with TVT-O resulted in a significantly lower risk of vaginal perforation than was seen with the outside-in TOT (OR: 0.21, $P<0.001$).

VII. TVT-EXACT & TVT-ABBREVO

Since the original development of the TVT and TVT-O devices, Ethicon has developed two new systems that represent the natural evolution of these devices. In the case of the TVT device, this came in the form of the TVT EXACT Continence System. In the case of the TVT-O, this came in the form of the TVT ABBREVO system.

TVT EXACT

Approximately 15 years after the development of the original TVT, the TVT EXACT continence system was introduced onto the market. The system was very similar to the original retropubic TVT system. The two major differences were that the diameter of the trocar (3.0 mm) was smaller than the original TVT and it was disposable. Otherwise the mesh sling implant itself was essentially the same as the original TVT. Many surgeons felt that the thinner trocar made it easier to pass the trocar behind the pubic bone. Otherwise, as would be expected, the clinical outcomes with this system appear to be comparable to the original. One-year cure rates have been reported as 94.5%, with a 0% vaginal mesh erosion rate (Aniuliene 2015). Subjective outcomes were also very good with results noted as either “Excellent” or “Good” in 93.4% of patients.

TVT ABBREVO

Unlike the EXACT, the trocar of the TVT ABBREVO is essentially the same as that of the original TVT-O. The biggest difference is instead the length of the sling. While the material and other dimensions of the sling are essentially the same as the original, the TVT ABBREVO sling length is substantially shorter (12cm) (Waltregny 2012). The reasoning behind this change was to have the tension-free support of the sling be similar to the original by penetrating the

obturator membrane, but then not have any additional sling material implanted in the muscle and subcutaneous tissue of the groin. Studies comparing these two systems suggest that this system achieved that goal. In a prospective RCT comparing the ABBREVO system to the original TVT-O, following 175 patients for one year, the authors found the cure rate to be 90.7% vs 91.7% (p=0.824) respectively (de Leval 2011). Likewise, anatomic cadaver studies demonstrated that the revised tape length consistently traversed the obturator membrane, while overall inserting less mesh on each side of the body as compared to the original TVT-O (Hinoul 2011) and avoided the obturator nerve and its branches (Hubka 2016). Subsequent studies of the ABBREVO system confirmed these early findings of good safety and efficacy (Capobianco 2014, Canel 2015, Shaw 2015, Li 2016, Tommaselli 2016, Kurien 2017). Overall the TVT ABBREVO system demonstrates comparable outcomes to the original TVT-O, with TVT ABBREVO system having less immediate short-term pain in some studies.

Summary of Conclusions of TVT EXACT & ABBREVO Data

The overall conclusion regarding the safety and efficacy of the TVT EXACT and ABBREVO procedures, is that these modified procedures are comparable to the original TVT and TVT-O procedures.

Signed: 

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Appendix A - TVT RCT References

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